

● INVITED REVIEW

Δ N-Bcl-xL, a therapeutic target for neuroprotection

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Abstract

The B-cell lymphoma-extra large (Bcl-xL) is a mitochondrial anti-apoptotic protein that plays a role in neuroprotection. However, during excitotoxic stimulation, Bcl-xL undergoes caspase-dependent cleavage and produces a fragmented form, Δ N-Bcl-xL. Accumulation of Δ N-Bcl-xL is associated with mitochondrial dysfunction and neuronal death. Therefore, strategies to inhibit the activity or formation of Δ N-Bcl-xL protect the brain against excitotoxic injuries. Our team found that the pharmacological inhibitor ABT-737 exerts dose dependent effects in primary neurons. When primary hippocampal neurons were treated with 1 μ M ABT-737, glutamate-mediated mitochondrial damage and neuronal death were exacerbated, whereas 10 nM ABT-737, a 100-fold lower concentration, protected mitochondrial function and enhanced neuronal viability against glutamate toxicity. In addition, we suggested acute vs. prolonged formation of Δ N-Bcl-xL may have different effects on mitochondrial or neuronal functions. Unlike acute production of Δ N-Bcl-xL by glutamate, overexpression of Δ N-Bcl-xL did not cause drastic changes in neuronal viability. We predicted that neurons undergo adaptation and may activate altered metabolism to compensate for Δ N-Bcl-xL-mediated mitochondrial dysfunction. Although the detailed mechanism of ABT-mediated neurotoxicity neuroprotection is still unclear, our study shows that the mitochondrial membrane protein Δ N-Bcl-xL is a central target for interventions.

Key Words: B-cell lymphoma-extra large; Δ N-Bcl-xL; mitochondria; ABT-737

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Introduction

The B-cell lymphoma-extra large (Bcl-xL) is a mitochondrial protein and a member of the Bcl2 family. It plays anti-apoptotic functions by preventing oligomerization of pro-apoptotic Bax and Bak (Cheng et al., 1996; Sattler et al., 1997; Ivanovska et al., 2004; Soane et al., 2008), reducing cytochrome c release (Kharbanda et al., 1997; Kim et al., 1997; Carthy et al., 2003) and regulating caspase activity (Zaidi et al., 2001; Bruey et al., 2007). In addition to its significance in cell survival, Bcl-xL is reported to play critical roles in neurophysiology by controlling intracellular energy metabolism, mitochondrial and other intracellular membrane dynamics, and neuronal growth. Bcl-xL enhances mitochondrial adenosine triphosphate (ATP) production by decreasing unnecessary proton leakage across the mitochondrial inner membrane via direct interaction with F₁F₀ ATP synthase (Alavian et al., 2011; Chen et al., 2011). It also promotes synaptic vesicle endocytosis and regulates homeostasis of synaptic vesicle pools; these functions are required for normal neurotransmission (Li et al., 2013). Bcl-xL promotes neurite outgrowth and branching (Park et al., 2015); thus it protects from the loss of axons and dendrites during neurotoxic insults and it supports proper synapse formation (Li et al., 2008).

Neuroprotection via Δ N-Bcl-xL Regulation

Despite its neuroprotective roles, Bcl-xL also participates in the promotion of neuronal death. Full length Bcl-xL protein contains caspase dependent cleavage sites within its N-terminus (Clem et al., 1998). Accumulation of a fragmented

form of Bcl-xL, Δ N-Bcl-xL, is associated with mitochondrial injury, or neuronal injury in both *in vitro* and *in vivo* models of cerebral ischemia (Jonas et al., 2004, 2005; Ofengeim et al., 2012; Park et al., 2017). Application of recombinant Δ N-Bcl-xL protein within the presynaptic terminal induces abnormally large mitochondrial membrane conductance (Jonas et al., 2004). Recombinant Δ N-Bcl-xL protein also forms mitochondrial pores and enhances the release of apoptogenic factors including cytochrome c (Basañez et al., 2001). In addition to the effects of recombinant Δ N-Bcl-xL protein, we have found that glutamate-mediated excitotoxicity and ischemic stroke enhance the formation of endogenous Δ N-Bcl-xL in hippocampal neurons; this event leads eventually to neuronal death (Ofengeim et al., 2012; Park et al., 2017). Therefore, strategies that prevent Δ N-Bcl-xL appearance, activity, or accumulation in the neurons have been found to be neuroprotective. Δ N-Bcl-xL may be an important therapeutic target in the treatment of brain injury caused by cerebral ischemia or neurodegenerative diseases.

The most recent study from our laboratory reported that application of the pharmacological inhibitor, ABT-737, prevents Δ N-Bcl-xL-mediated neurotoxicity (Park et al., 2017). Our *in silico* model shows that cleavage of the Bcl-xL N-terminus does not alter ABT-737 binding sites, thus Δ N-Bcl-xL can form a complex with ABT-737. Although ABT-737 interacts with both full length and Δ N-Bcl-xL, the binding affinity to each protein may be different. BH3 containing proteins Bak or Bad are capable of binding to the BH1, BH2 and BH3 pocket of the 3-dimensional structure of Bcl-xL

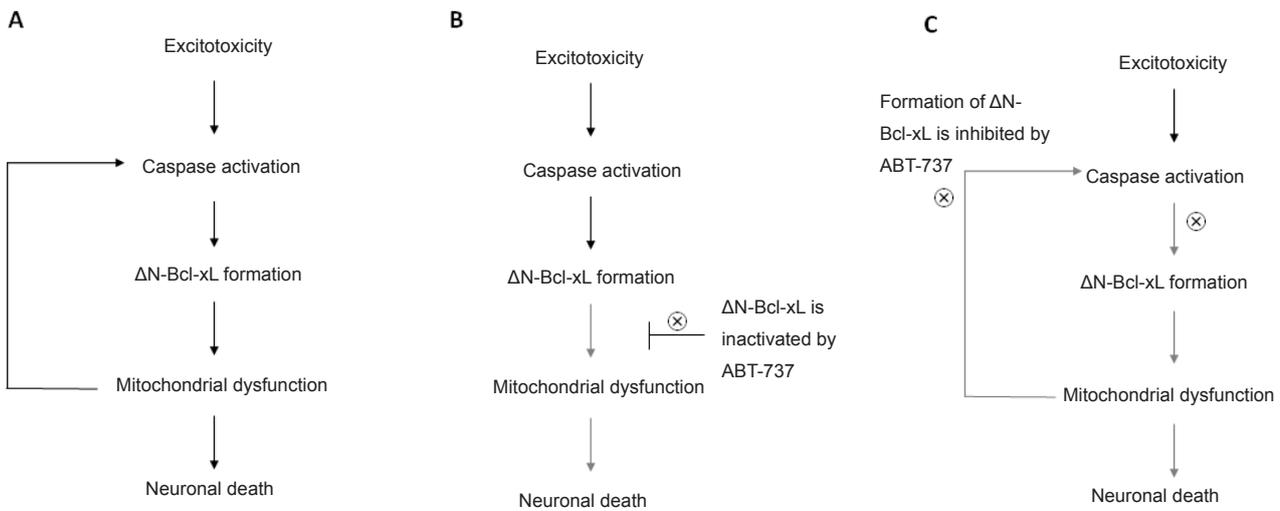


Figure 1 ABT-737 inhibits activity and formation of Δ N-Bcl-xL.

(A) Excitotoxic stimulation caused by cerebral ischemia triggers caspase-dependent cleavage of Bcl-xL and forms Δ N-Bcl-xL. Accumulation of Δ N-Bcl-xL at the inner membrane leads to mitochondrial dysfunction associated with mPTP opening and cytochrome c release, then eventually causes neuronal death. (B) Excitotoxic stimulation produces Δ N-Bcl-xL protein, but ABT-737 binds with the active site of Δ N-Bcl-xL, therefore inactivates neurotoxic functions of Δ N-Bcl-xL at the mitochondria (the immediate mechanism of action of ABT-737). (C) Inactivation of Δ N-Bcl-xL by ABT-737 blocks mPTP opening and cytochrome c release which eventually inhibits caspase activation (delayed function of ABT-737). Therefore, application of ABT-737 also blocks formation of Δ N-Bcl-xL. Bcl-xL: B-cell lymphoma-extra large; mPTP: mitochondrial permeability transition pore.

(Sattler et al., 1997). ABT-737 is a BH3 mimetic; it may interact with Bcl-xL similarly to Bak or Bad. Since full-length Bcl-xL contains a BH4 domain that is removed by caspase cleavage, creation of Δ N-Bcl-xL from full length Bcl-xL may expose the binding sites, thus Δ N-Bcl-xL may have a higher efficiency to form the ABT-737- Δ N-Bcl-xL complex compared to full length Bcl-xL. In neurons treated with a low concentration of ABT-737, Δ N-Bcl-xL may be preferentially targeted compared to full length Bcl-xL, while a high concentration of ABT-737 blocks both anti-apoptotic full length and pro-apoptotic cleaved Δ N-Bcl-xL. Although we have not investigated the mechanism of Δ N-Bcl-xL-ABT-737 binding in detail, we nevertheless predict that Δ N-Bcl-xL undergoes conformational changes after losing the N-terminus or upon binding to mitochondrial membranes. The new conformation of Δ N-Bcl-xL may be more accessible to ABT-737, presumably by exposing the hydrophobic groove that contains ABT-737 binding sites (Lee et al., 2007).

Our data show that ABT-737 exerts dose dependent effects in primary hippocampal neurons. At a high concentration, ABT-737 exacerbates glutamate-induced mitochondrial dysfunction and neuronal death. However, at a low concentration, it conserves mitochondrial function and protects neurons against excitotoxic insult by blocking pro-apoptotic functions of Δ N-Bcl-xL. We further report that Δ N-Bcl-xL is located at both the outer and inner membranes of mitochondria, and that it directly alters mitochondrial inner membrane potential. Our data suggest that application of ABT-737 prevents Δ N-Bcl-xL-mediated mitochondrial dysfunction and neuronal death by multiple pathways

(Figure 1). An immediate mechanism of ABT-737's action is to bind directly to Δ N-Bcl-xL, inactivating it and protecting mitochondrial membranes from injury. In addition to sequestering already formed Δ N-Bcl-xL, prevention of the appearance of Δ N-Bcl-xL by ABT-737 also attenuates traditional apoptotic cascades mediated by, for example, the mitochondrial permeability transition pore, cytochrome c release and caspase activation; these actions of ABT-737 eventually block more Δ N-Bcl-xL production by caspases by inhibiting a positive feedback loop. Together, ABT-737 prevents the function of Δ N-Bcl-xL both by inhibiting its activity and blocking its formation (Figure 1).

In addition to our current publication (Park et al., 2017), various approaches to protect the brain by preventing Δ N-Bcl-xL action have been reported previously. Ofengeim et al. (2012) reported neuroprotective properties of ABT-737 in an *in vivo* system. The authors found that stereotaxic injection of ABT-737 before or after 4 vessel occlusion protected CA1 hippocampal neurons from ischemia-induced cell death. This study also showed that Δ N-Bcl-xL is capable of triggering cell death under conditions of Bax or Bak depletion indicating that Δ N-Bcl-xL-mediated cell death mechanisms may occur independently of traditional Bax or Bak mediated cell death pathways. Application of ABT-737 attenuated ischemia-induced large-channel opening in mitochondrial membranes and reduced the number of degenerating neurons in the hippocampus. Miyawaki et al. (2008) reported that in ischemic preconditioning, where a short exposure of ischemia prior to the main ischemic event protects rodent brains, the conversion of procaspase 3 to

form the active caspase 3 in CA1 pyramidal neurons was attenuated. They further found that prevention of formation of Δ N-Bcl-xL was correlated with decreased activation of caspase 3, suggesting that preconditioning protects neurons from apoptotic death through inhibition of the onset of the positive feedback loop of caspase activation and full length Bcl-xL cleavage. In investigating Bcl-xL binding partners that potentially interfere with Bcl-xL cleavage, Arena et al. (2013) reported that PTEN-induced putative kinase 1 (PINK1) binds to Bcl-xL. Interaction between PINK1 and Bcl-xL causes Bcl-xL phosphorylation which impairs cleavage of Bcl-xL's N terminus thereby exerting protection against apoptotic stimulation.

Our current publication also demonstrates the effect of prolonged Δ N-Bcl-xL exposure in the primary hippocampal neurons through a system of exogenous Δ N-Bcl-xL overexpression in addition to glutamate-mediated acute endogenous Δ N-Bcl-xL formation (Park et al., 2017). Unlike during acute Δ N-Bcl-xL formation, over expression of Δ N-Bcl-xL alone did not demonstrate dramatic neurotoxicity. Neurons overexpressing Δ N-Bcl-xL did not die even over 2 weeks of overexpression in our study. During neuronal development, neurons may undergo adaptation to compensate for Δ N-Bcl-xL-mediated mitochondrial dysfunction to retain their survival. Despite having no significant change in viability, however, Δ N-Bcl-xL overexpressing neurons demonstrated a reduced mitochondrial potential. It is still unclear if Δ N-Bcl-xL-mediated mitochondrial potential loss is exclusively due to alteration of mitochondrial inner membrane leak or due to cytochrome c release and the inability to generate a mitochondrial membrane potential. Nevertheless, we expect that Δ N-Bcl-xL-induced inner membrane depolarization may cause the onset of mitochondrial fission and mitophagy, the latter of which is the degradation or self-digestion of mitochondria. In another proposed function for Bcl-xL in mitophagy, Maiuri et al. (2007) and Pedro et al. (2015) reported that the interaction between Bcl-xL and the pro-autophagic protein Beclin-1 suppresses autophagy, but that the BH3 protein Bad and other BH3-containing proteins induce autophagy by causing a disassociation of Beclin-1 from Bcl-xL. The BH3 mimetic ABT-737 also inhibits Beclin-1/Bcl-xL interaction and enhances autophagy (Malik et al., 2011). Since Δ N-Bcl-xL is a BH3 containing fragment, Δ N-Bcl-xL could also play the part of the BH3-only proteins or mimetics in causing a disassociation of Beclin-1 from its inhibitory binding partners. Prolonged exposure to Δ N-Bcl-xL (12–14 days of transfection) could induce formation of autophagosomes containing mitochondria thus initiating mitochondrial degradation. It is known that inhibition of apoptosis may shift the balance to other forms of cell death/survival, including autophagy/mitophagy (Lalaoui et al., 2015; Radogna et al., 2015; White, 2015), therefore we suggest that Δ N-Bcl-xL overexpression in the absence of death-inducing stimuli may tip the balance toward autophagy as a survival mechanism. Gustafsson's

group also reported involvement of the BH3 protein, Bnip3 in mitochondrial autophagy. Bnip3 induces translocation of Parkin, a ubiquitin ligase that is downstream of PINK1. Parkin-expressing mitochondria then enter autophagosomes (Lee et al., 2011; Rikka et al., 2011). Mitophagy due to Parkin accumulation has been reported in glutamate-induced excitotoxicity (Van Laar et al., 2015). Various studies reported that defects in mitophagy are associated with other neurological disorders (Youle and Narendra, 2011; Scott et al., 2017), and regulation of mitophagy homeostasis controls survival or recovery of neurons (Amato et al., 2017; Zhan et al., 2017; Zhang et al., 2017).

Conclusion

In summary, our results support that production of Δ N-Bcl-xL by cleavage of full length Bcl-xL controls mitochondrial inner membrane dynamics (e.g., mitochondrial permeability transition and mitochondrial membrane potential). In addition, Δ N-Bcl-xL interaction with the inner mitochondrial membrane may induce mitochondrial remodeling in surviving neurons presumably *via* mitophagy during neuronal development or during prolonged low level excitotoxic exposure. Together, arresting Δ N-Bcl-xL activity, production or accumulation protects the brain from neurotoxic insults but may prevent the activation of autophagic pathways, therefore, we suggest that Δ N-Bcl-xL is a novel but complex therapeutic target to treat brain injuries that are relevant to stroke, Alzheimer's and Parkinson's diseases.

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Open peer review report:

Reviewer: Ryan Hirschi, University of Utah, USA.

Comments to authors: This paper describes a novel yet complex therapeutic target to treat brain injuries relevant to common neurological disorders. Overall, the article is well written and provides a good overview of previously published work. References are abundant and appropriate. The topic is interesting and the findings are novel.

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